IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	**Confirmation No. 7108**
FEASTER, *et al.*	Art Unit: 1657
Serial No.: 10/763,339	Examiner: Bin Shen
Filed: 26 January 2004	Atty. Dckt: 034047.003DIV1 WRAIR 00-23B
For: DEVICE FOR DETECTING, MEASURING AND MONITORING THE ACTIVITIES AND CONCENTRATIONS OF PROTEINS	

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Mail Stop: AF

Dear Sir:

Applicant(s) respectfully request(s) review of the final rejection in the above-identified application. No amendments are being filed with this request.

This Request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

I am attorney of record.

Respectfully submitted,

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Date: 8 September 2011
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REASONS FOR REVIEW REQUEST

The Claimed Invention

The claimed invention is a device for detecting, measuring or monitoring the activities of at least one protein (n = number of proteins) in a test sample, where the protein belongs to a plurality of proteins which have similar or overlapping properties towards a plurality of substrates. The claimed device comprises a cartridge which itself comprises n+1 number of substrates. Thus, the claimed device itself must comprise at least two substrates contained therein.

The substrates are contacted with the sample to be assayed and the activity or the concentration of the protein is measured based on the reaction rates between the protein and each of the substrates taking into account the particular sensitivity coefficient of the protein.[1]

The Issue and Law

INVENTION AS A WHOLE – Whether an invention is unobvious when the references cited by an examiner do not teach or suggest the invention, i.e. a device having a cartridge which comprises n+1 substrates for which n protein(s) to be assayed have similar or overlapping properties towards, as a whole.

LAW: In order to be obvious, the cited documents must teach or suggest the invention as a whole. See 35 U.S.C. 103(a), *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983) *aff'd mem.* 738 F.2d 453 (Fed. Cir. 1984, *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350 (U.S. 2007); and *Abbott Laboratories v. Sandoz, Inc.*, No. 05 C 5373 (N.D.Ill. 2007) ("KSR … did not mention or affect the requirement that each and every claim limitation be found present in the combination of the prior art references before the [103 obviousness] analysis proceeds").

The Facts

In the Office Action mailed 9 May 2011, the Examiner rejected claims 29, 30, 35 and 39-43 under 35 U.S.C. 103(a) as being unpatentable over London (1995) in view of Worek (1999) and Jacobs (1993). In making the rejection, the Examiner noted that London does not teach at least two substrates in a cartridge of a device. The Examiner, however, (incorrectly) interpreted the disclosure of Worek as teaching the use of two different substrates to determine acetylcholinesterase (AChE) activity in a sample and Jacobs as teaching a device with an

[1] It is noted that claims to the method were issued in U.S. Patent No. 6,746,850 as the cited documents of record did not teach or suggest the sensitivity coefficient as set forth in the claims.

insertable cartridge such that the Examiner deemed that one of ordinary skill in the art would have been motivated to combine the disclosures to obtain a device comprising a cartridge containing at least two substrates in order to measure the activity or concentration of a given protein.

In the Response filed 5 August 2011, Applicants explained in detail the reasons why not one of the cited documents, alone or in combination, teaches or suggests a device comprising a cartridge containing at least two substrates in order to measure the activity or concentration of a given protein as set forth in the instant claims. Applicants explained in detail why Worek (as well as Jacobs) does not alleviate the deficiencies of London.

In the Advisory Action mailed 31 August 2011, the Examiner found Applicants' arguments unpersuasive because she (1) does not give the number of substrates contained in the cartridge any patentable weight as she (incorrectly) correlates its scope and meaning to an intended use, i.e. "to measure n number of proteins", and (2) incorrectly misinterprets Table 1 of Worek as teaching that two substrates, i.e. both ASCh and BSCh, are used to determine the activity of one protein, i.e. AChE (or BChE).

(1) Not an intended use limitation

Applicants respectfully submit that the number of substrates in the cartridge as instantly claimed is an actual structural limitation. Specifically, independent claims 29, 42 and 43 specifically require that the cartridge contains at least two substrates (an always one more substrate than the number of proteins being assayed). The limitation of at least two substrates (and one more substrate than the number of proteins being assayed) is an actual tangible structural feature of the claimed device. In other words, the device according to the instant invention will always contain two or more substrates in its cartridge. The fact that one may intend to use the device to measure one protein or more than one protein does not diminish the requirement that the device must have at least two substrates contained therein.

Therefore, the n+1 number of substrates contained in the cartridge of the claimed device must be given patentable weight.

(2) Incorrect misinterpretation of Table 1 of Worek

The Examiner either misinterprets or misunderstands the disclosure, including Table 1, of Worek. Specifically, the Examiner incorrectly reads Table 1 of Worek as teaching or suggesting

that both the substrates ASCh and BSCh are used to determine the activity of each cholinesterase (AChE and BChE). For the convenience of the Panel, Table 1 of Worek is as follows:

Table 1
Standard procedure for the determination of AChE and BChE activities

	AChE	BChE	Final conc.
Pipetted in polystyrol cuvets:			
Phosphate buffer (0.1 mol/l, pH 7.4)	2.000 ml	3.000 ml	100 mM
DTNB (10 mmol/l)	0.100 ml	0.100 ml	0.30 mM
Ethopropazine (6 mmol/l)	0.010 ml	–	0.02 mM
Hemolysate (whole blood 1:100)	1.000 ml	–	
Plasma (undiluted)	–	0.010 ml	
Equilibrate at 37°C for 10 min, then add:			
ASCh (28.4 mmol/l)	0.050 ml	–	0.45 mM
BSCh (63.2 mmol/l)	–	0.050 ml	1.00 mM
Read the color development for 3 min at 37°C and 436 nm ($\varepsilon = 10.6 \times 10^3\ M^{-1}\ cm^{-1}$)			

This incorrect reading of Table 1 of Worek is plainly evident by the data/parameters set forth in the table itself. Specifically, the amounts of reagents indicated in the column below AChE is for the assay for AChE activity and the amounts of reagents indicated in the column below BChE is for the assay for BChE activity. The dashes indicate that the given reagent was not used in the particular assay. This is evidenced by the fact that AChE is the cholinesterase mainly found in red blood cells, i.e. hemolysate, and BChE is mainly found in plasma. One will note that for the AChE assay, only one substrate, i.e. ASCh, is used (as there is no BSCh added) and for the BChE assay, only one substrate, i.e. BSCh, is used (as there is no ASCh added). This is evidenced by the amounts indicated in the column providing the final concentrations of each of the reagents in the given assay. In particular, one will note that the total volume of the assay mixtures both AChE and BChE are 3.16 ml. The final volume of each assay is obtained by adding the volumes in a given column, i.e.

AChE	BChE
2.000 ml	3.000 ml
0.100 ml	0.100 ml
0.010 ml	–
1.000 ml	–
–	0.010 ml
0.050 ml	–
– = 3.16 ml	and 0.050 ml = 3.16 ml.

The final concentration in mM for a given reagent in the reaction mixture is obtained by first converting the indicated volume of the given reagent to liters, then multiplying it by the indicated mmol/l, and then dividing it by the total reaction volume (in liters). For example, the final concentration of 0.30 mM of DTNB in the reaction mixture is obtained as follows:

0.100 ml x (1 L/1000 ml) = 0.0001 L x (10 mmol/L) = 0.001 mmol and

0.001 mmol ÷ 0.003 L (total volume of the reaction mixture) = 0.30 mM DTNB.

Obviously, since a dash is indicated in the BChE column for ethopropazine, the BChE reaction mixture does not contain 0.02 mM of ethopropazine in the final reaction mixture.

The fact that both ASCh and BSCh are not used in one reaction mixture for either AChE or BChE is plainly evident by the final concentrations. Specifically, 0.050 ml of 28.4 mmol/L ASCh gives 0.45 mM and 0.050 ml of 63.2 mmol/L BSCh gives 1.00 mM. If both ASCh and BSCh were used for each cholinesterase then one of two final concentrations would result. The first one would be based on the final reaction volume being 3.21 ml rather than 3.16 ml because 0.050 ml would have to be added thereto. A final volume of 3.21 ml would give a final concentration of ASCh of 0.44 mM and 0.98 mM of BSCh. The other possible result would be based on adding all the indicated amounts in both columns to give a final reaction volume of 6.32 ml. This would give 0.22 mM ASCh and 0.50 mM BSCh. Neither one of the two resulting concentrations is provided in the final concentration column. Thus, it is clear to a skilled person that Table 1 combines the reaction parameters of two separate assays into one table, but doing so does not in any way teach or suggest to one of ordinary skill in the art that both substrates should be used to measure the activity of one cholinesterase. In other words, Table 1 is correctly interpreted as setting forth two separate and distinct assays as follows:

Assay 1 for AChE

	AChE	Final conc.
[redacted] in polystyrol cuvets:		
Phosphate buffer (0.1 mol/l, pH 7.4)	2.000 ml	100 mM
DTNB (10 mmol/l)	0.100 ml	0.30 mM
Ethopropazine (6 mmol/l)	0.010 ml	0.02 mM
Hemolysate (whole blood 1:100)	1.000 ml	
Plasma (undiluted)	-	
Equilibrate at 37°C for 10 min, then add:		
[redacted]h (28.4 mmol/l)	0.050 ml	0.45 mM
[redacted] at 37°C and 436 nm ($\varepsilon = 10.6 \times 10^3\ M^{-1}\ cm^{-1}$)		
Final Volume =	3.16 ml	

Assay 2 for BChE

	BChE	Final conc.
[redacted] in polystyrol cuvets:		
Phosphate buffer (0.1 mol/l, pH 7.4)	3.000 ml	100 mM
DTNB (10 mmol/l)	0.100 ml	0.30 mM
Ethopropazine (6 mmol/l)	-	
Hemolysate (whole blood 1:100)	-	
Plasma (undiluted)	0.010 ml	
Equilibrate at 37°C for 10 min, then add:		
[redacted] (63.2 mmol/l)	0.050 ml	1.00 mM
[redacted] at 37°C and 436 nm ($\varepsilon = 10.6 \times 10^3\ M^{-1}\ cm^{-1}$)		
Final Volume =	3.16 ml	

Thus, it is clear that Worek does not teach or suggest using both ASCh and BSCh to assay one cholinesterase. Therefore, Worek does not teach or suggest employing at least two substrates to assay one protein. Consequently, there is nothing in any of the documents cited by the Examiner that teaches or suggests a device for measuring the concentration or activity of at least one protein by using at least two substrates (and always one more substrate than the number of proteins being assayed). Since the cited documents, when correctly interpreted, do not teach or suggest the claimed invention as a whole, the claimed invention is unobvious.

Therefore, Applicants respectfully request that the review panel either find the claims allowable or reopen prosecution. If the review panel decides to reopen prosecution, Applicants would appreciate a proposed amendment if appropriate.